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VIEWPOINT

Lipoprotein(a) as a Potential Causal Genetic Risk Factor of Cardiovascular Disease

A Rationale for Increased Efforts to Understand its Pathophysiology and Develop Targeted Therapies

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Recent published studies have provided increasing evidence that lipoprotein(a) [Lp(a)] may be a potential causal, genetic, independent risk factor for cardiovascular disease (CVD). Lp(a) levels >25 mg/dl are present in ~30% of Caucasians and 60% to 70% of Blacks. Lp(a) is composed of apolipoprotein B-100 and apolipoprotein (a) [(apo(a)]. Circulating Lp(a) levels are primarily influenced by the *LPA* gene without significant dietary or environmental effects, mediating CVD risk throughout the patient's lifetime. Recent clinical outcomes studies, meta-analyses, and Mendelian randomization studies, in which randomization of Lp(a) levels is achieved through the random assortment of *LPA* gene variants thereby removing confounders, have shown that genetically determined Lp(a) levels are continuously and linearly related to risk of CVD. Currently, Lp(a) pathophysiology is not fully understood, and specifically targeted therapies to lower Lp(a) are not available. We provide a rationale for increased basic and clinical investigational efforts to further understand Lp(a) pathophysiology and assess whether reducing Lp(a) levels minimizes CVD risk. First, a detailed understanding of Lp(a) synthesis and clearance has not been realized. Second, several mechanisms of atherogenicity are known to varying extent, but the relative contributions of each are not known. Lp(a) may be atherothrombotic through its low-density lipoprotein moiety, but also through apo(a), including its ability to be retained in the vessel wall and mediate pro-inflammatory and proapoptotic effects including those potentiated by its content of oxidized phospholipids, and antifibrinolytic effects. Finally, development of specific Lp(a)-lowering agents to potently lower Lp(a) will allow testing of mechanistic hypotheses in animal models and the design of randomized clinical trials to assess reduction in CVD. A convergence of academic, scientific, pharmaceutical, and National Institutes of Health priorities and efforts can make this a reality in the next decade. (J Am Coll Cardiol 2012;60:716–21) © 2012 by the American College of Cardiology Foundation

Cardiovascular disease (CVD) mediated by atherosclerosis is initiated very early in human life and manifests itself clinically after a long latent phase of integrative and cumulative insults to the vessel wall by genetic, environmental, behavioral, and dietary risk factors. A hallmark of atherosclerosis is chronic inflammation mediated by innate and adaptive immune responses in removing the accumulation of pro-inflammatory substances. These responses are manifested primarily by the presence of activated macrophages, T-cells, and humoral responses such inflammatory cytokines (1). Although a variety of pro-inflammatory materials accumulate in the vessel wall, modified and oxidized products of apoB-containing lipoproteins, representing danger-associated molecular patterns (2), are key mediators of such pro-inflammatory responses. Without accumulation of modified lipids in the vessel wall, primary inflammatory mechanisms would likely contribute little to clinical manifestations of CVD.

Broadly speaking, there are 4 major categories of lipid abnormalities in humans: elevated low-density lipoprotein cholesterol (LDL-C), low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and elevated lipoprotein(a) [Lp(a)]. LDL-C, HDL-C, and triglyceride levels are affected by diet. By contrast, Lp(a) plasma levels are mediated largely by the *LPA* gene locus present on chromosome 6q22–23, with small-to-negligible effects of diet (3). Lp(a) levels >50 mg/dl represent a prevalence >80th percentile (reviewed in Nordestgaard et al. [4]), which is typically considered to be "elevated" for clinical biomarkers. However, most studies and meta-analyses show an increase

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in CVD risk starting at Lp(a) >25 mg/dl (5). It is estimated that Lp(a) levels >25 to 30 mg/dl are present in approximately 30% of Caucasians and 60% to 70% of Blacks (i.e., ~100,000,000 Americans). Because elevated Lp(a) levels are present at birth, they may potentially contribute to CVD risk starting very early in life, analogous to other genetic risk factors.

Although the mortality from CVD has significantly declined since the 1960s, there is no convincing data that the development of CVD has declined in proportion. The residual risk represented by lipid abnormalities remains high and is the continuing focus of novel treatments for raising HDL-C and lowering triglycerides. As supported by recent studies and the current paper by Helgadottir et al. (6) in the current issue of the *Journal*, the independent residual risk of Lp(a) in mediating CVD is substantial and represents a significant opportunity and potential target of therapy in reducing the overall risk of CVD even further.

What is Lp(a)? Lp(a) is a circulating lipoprotein composed of liver-derived apo(a) covalently bound to apoB, which is similar in lipid composition to apoB of LDL (7). In 1963, Kare Berg (8) reported the presence of Lp(a) in humans when searching for antigenic determinants of blood types by observing that one-third of patients' plasma reacted to an antiserum from rabbits immunized with human LDL. From 1987, Richard Lawn and associates (9) discovered that the *LPA* gene, and thus the protein apo(a), was highly homologous to plasminogen. Plasminogen contains 5 kringles and a protease domain that is acted upon by plasminogen activators, either endogenously or therapeutically, to generate plasmin and initiate fibrinolysis. Apo(a) has important differences compared with plasminogen: 1) apo(a) has an unpaired cysteine and forms a disulfide bond with apoB to generate the lipoprotein particle Lp(a); 2) it contains an inactive protease domain potentially acting as a competitive inhibitor; and 3) it lacks kringles 1 to 3 of plasminogen, but contains kringle 5 (KV) and 10 subtypes of KIV, of which KIV-II is present in multiple repeats (over 40 unique isoforms exist), giving LPA/apo(a) the distinction of being one of the most polymorphic genes/proteins in nature. In fact, 80% of patients have 2 distinct isoforms, that is, 2 different-sized circulating Lp(a) particles. Interestingly, Lp(a) is only present in humans, apes, and Old World monkeys, but a second version containing only multiple copies KIII bound to apoB evolved separately in the European hedgehogs. This suggests that the plasminogen gene independently remodeled twice during mammalian evolution to produce similar forms of apo(a)/Lp(a) in 2 widely divergent groups of species, perhaps reflecting important physiological, though not yet revealed, advantages.

Plasma Lp(a) levels are inversely associated with the size of the apo(a) isoforms, which can explain up to 50% of plasma-level variability. Patients of African ancestry generally have 2- to 3-fold higher Lp(a) levels for the same number of KIV-II repeats than Caucasians, an observation that has not been fully explained (10). A second layer of plasma-level variability is added by *LPA* single nucleotide polymorphisms (SNPs) that can be associated with both higher and lower Lp(a) levels (11,12). Significant associations exist between two *LPA* variants, rs10455872 and rs3798220, increased Lp(a) levels, and CVD with the CVD risk primarily mediated by Lp(a) levels rather than an independent effect of the SNPs (11,12). These SNPs correlate with a smaller apo(a) isoform size and, account for an additional 36% of the total variation in Lp(a) levels. The underlying mechanisms through which these SNPs result in higher Lp(a) levels are not known.

Abbreviations and Acronyms

apo(a) = apolipoprotein(a)
CVD = cardiovascular disease
HDL-C = high-density lipoprotein cholesterol
K = kringle
LDL-C = low-density lipoprotein cholesterol
Lp(a) = lipoprotein(a)
OxPL = oxidized phospholipids
SNP = single nucleotide polymorphism

Measurement of Lp(a) levels is offered by a variety of manufacturers, is not fully standardized, and is performed with several assays, including immunoturbidometry, nephelometry, and enzyme-linked immunosorbent assays. Assays can be reported as nmol/l using a World Health Organization–approved, International Federation of Clinical Chemistry and Laboratory Medicine reference standard apo(a) with 21 KIV repeats and value of 107 nmol/l (13). This assay measures Lp(a) as moles of apo(a) protein using specific monoclonal antibodies (14), is independent of isoform size, will facilitate comparison among studies, and should be the preferred method. Lp(a) can also be measured as mg/dl representing the entire mass of Lp(a) (protein, lipid, and carbohydrate). In assays reporting data as mg/dl, despite use of polyclonal antibodies independent of isoform size, apo(a) size-dependent bias can be seen with the assay calibrators, which are generally pooled plasma samples that putatively represent all the different isoforms in the plasma being measured. Therefore, these assays must be validated with reference standards. Lp(a) can also be measured as Lp(a) "cholesterol" in mg/dl and assayed using quantification gradient analysis, but the published database for the predictive value of this assay is significantly smaller than the others. In general, nmol/l can be converted to mg/dl by dividing by 2.8, and Lp(a) "cholesterol" values are normal when <10 mg/dl. See Koschinsky and Marcovina (15) for a detailed review on Lp(a) measurements.

What is the contribution of Lp(a) to genetic risk of CVD and specifically atherothrombosis? The study from Helgadottir et al. (6) encompassing nearly 45,000 patients, published in this issue of the *Journal*, suggests that *LPA* variants rs10455872 and rs3798220, defined as an LPA risk score by combining their effects, are associated with angiographically determined earlier onset of coronary artery disease ($p = 4.8 \times 10^{12}$), peripheral arterial disease ($p = 2.9 \times 10^{14}$), aortic aneurysm ($p = 6.0 \times 10^{5}$), and ischemic stroke subtype large artery atherosclerosis ($p = 6.7 \times 10^{4}$).

Importantly, these effects were present in Caucasians and also in African-Americans, which has been an area of controversy (16). As opposed to the effect on anatomical presence of CVD, there was no effect of these SNPs on venous thrombosis or early atherogenesis as measured by carotid intima-media thickness, suggesting that the major effect of Lp(a) is on advanced plaque development and destabilization rather than thrombosis. There was also no effect of *LPA* variants on ischemic stroke subtypes, cardioembolism, small vessel disease, or intracranial aneurysm. However, as noted by the authors (6), the study may have been underpowered to detect significance within these groups. Finally, Lp(a) levels were not measured, which would have been useful to tease out the effect of the SNPs on Lp(a) levels and their respective effects on CVD risk.

Within the last few years, multiple studies have shown that elevated Lp(a) levels are independently and linearly predictive of future CVD (5,12,16–19). For example, in the Copenhagen City Heart Studies of 42,000 subjects with a 15-year follow-up (19) using a Mendelian randomization approach, Lp(a) levels were related to the number of genetically determined apo(a) KIV-II repeats, with an inverse association between decreasing number of KIV-II repeats in the *LPA* gene and higher plasma Lp(a) levels. In turn, higher levels were continuously related to risk of myocardial infarction. Although Mendelian randomization studies are not a proxy for randomized controlled trials in proving causality, they provide supporting evidence for a potential role of Lp(a) as a risk factor for CVD.

What are the biological mechanistic underpinnings of the atherogenicity of Lp(a)? The putative physiological role of Lp(a), if any, remains undefined, but it has been postulated to have roles in tissue healing, innate immunity, and infection. Apo(a) has potent lysine binding domains, similar to those on plasminogen, and binds to damaged endothelial cells and exposed or injured subendothelial matrix proteins, and delivers cholesterol for cell membrane growth. In a physiological setting without the presence of CVD risk factors, this property (now perhaps vestigial) may have contributed to the selection of Lp(a) in primates. Alternatively, it may also have been a random occurrence of gene duplication, although this appears less likely, having arisen independently 2 separate times. However, in a setting of CVD risk factors and increased oxidative and inflammatory stress present in our current societies, Lp(a) is clearly proatherogenic when levels are elevated. One mechanism of atherogenicity is through the LDL component. However, apo(a) alone, and Lp(a) as a lipoprotein, have additional potential contributions (20), including increasing endothelial cell permeability and expression of adhesion molecules, promoting smooth muscle cell proliferation, enhancing monocyte entry and retention in the vessel wall, macrophage foam cell formation, promoting release of pro-inflammatory IL-8 levels, and antifibrinolytic effects, as a carrier of pro-inflammatory and proatherogenic OxPL (21). Importantly, a recent study has documented that Lp(a) and OxPL mediate macrophage apoptosis in endoplasmic reticulum–stressed macrophages by signaling through the CD36/TLR2 receptor pathway to initiate ERK activation. ERK stimulates lysosomal p47 clustering and NADPH oxidase–dependent generation of reactive oxygen species (Fig. 1) (22). This is also consistent with data from our laboratory showing the presence of OxPL and Lp(a) in advanced "vulnerable" human carotid artery thin-cap fibroatheroma, which is the precursor to plaque rupture, demonstrating concomitant immunostaining for OxPL and apo(a) (23). Since macrophage apoptosis is a key component of plaque vulnerability, these data provide supporting evidence of Lp(a) as a risk factor for development of advanced, clinically relevant atherosclerotic lesions.

Interestingly, recent data demonstrate that OxPL are also present on plasminogen, which seems to represent the other major source of OxPL in plasma proteins. However, when present on plasminogen, OxPL actually potentiate, rather than inhibit fibrinolysis, and would be expected to be protective against excess thrombus formation (24). This suggests context-dependent and carrier-dependent roles of OxPL in mediating atherothrombosis (25).

A key component of the atherogenicity of Lp(a) has been the contribution of OxPL. OxPL are immunogenic and accumulate in atherosclerotic lesions and mediate plaque destabilization. Elevated levels of OxPL on apoB are associated with the presence and progression of coronary artery disease and peripheral arterial disease, predict new CVD events in prospective studies, and provide enhanced predictive value in models with established risk factors or Framingham Risk Score estimates (17,18,26) (reviewed in Taleb et al. [21]). Although strong in vitro data exist to support the role of Lp(a) in inhibiting fibrinolysis, including alteration of fibrin clot architecture, reducing plasmin generation and tissue factor pathway inhibitor and plasminogen activator-1 levels, the findings in the current study seem to refute a strong in vivo effect.

What are the gaps in the basic understanding of Lp(a) biology? The pathways regulating the synthesis and degradation of Lp(a) are not well understood. Lp(a) in plasma represents the summation of the production of apo(a) from both chromosomes. Lp(a) levels generally do not change significantly starting from a few months after birth unless there is an acute phase response, in which case they can rise abruptly (21). Because smaller apo(a) isoforms can be generated more quickly per unit time, small isoforms are associated with higher plasma Lp(a) levels. Clearance of Lp(a) is not well understood, but the LDL receptor or isoform size does not appear to be a main determinant of clearance. Putative receptors for Lp(a) have been proposed, as well as re-circulation (on/off) of apo(a) among LDL particles. Free apo(a) is not usually present in humans, except in patients with advanced renal failure, although they accumulate large rather than small isoforms. However, apo(a) fragments can be found in the urine of patients with

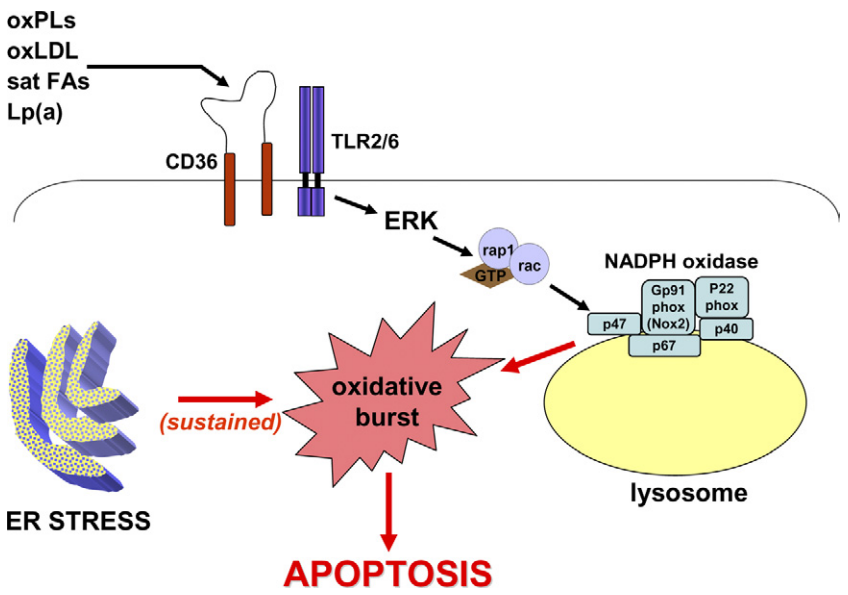

Figure 1 **Model Depicting Development of Macrophage Apoptosis, a Major Factor in Plaque Vulnerability, by Lp(a)/OxPL During ER Stress**

Various ligands for CD36 such as lipoprotein(a) [Lp(a)], oxidized phospholipids (OxPL), oxidized low-density lipoprotein (OxLDL), and saturated fatty acids (sat FAs) signal through CD36 and TLR2/6 to initiate ERK activation. ERK stimulates lysosomal p47 clustering and NADPH oxidase–dependent generation of reactive oxygen species (ROS) known as the oxidative burst. ROS generation is sustained by the presence of an endoplasmic reticulum (ER) stress–inducing agent and is essential for macrophage apoptosis induced by this pathway. Reprinted, with permission, from Seimon et al. (22).

unmeasurable Lp(a) levels, suggesting proteolytic cleavage as 1 clearance mechanism. A better understanding of the basic mechanisms of the production and metabolism of Lp(a) will be important in understanding Lp(a) biology and in defining the effect of future therapeutic agents.

Unlike the recent human data, data in animal models to define the atherogenicity of Lp(a) have been inconsistent due to the following limitations: 1) Lp(a) is not naturally present in experimental models such as mice and rabbits. To produce such models, double transgenic animals overexpressing both apo(a) and human apoB-100 [apo(a) does not bind to mouse apoB and therefore cannot generate true Lp(a) particles] need to be generated; 2) most constructs have cDNA rather than genomic DNA and therefore do not have the natural promoters; 3) most Lp(a) transgenic models, until recently (27), have expressed levels of Lp(a) that are considered in the normal range of humans (<25 mg/dl), and usually only 1 isoform is expressed, whereas over 40 isoforms exist in humans. Therefore, lack of appropriate experimental models has led to inadequate testing of hypotheses. New approaches to address these gaps in basic research are needed, including studies to understand apo(a) synthesis and metabolism in vivo, pro-inflammatory effects, novel animal models with genomic apo(a) constructs, basic studies on fibrinolytic and platelet effects, effects on macrophage apoptosis and foam cells formation, and the role of Lp(a)-associated components, such as OxPL and Lp-PLA_2 on atherogenicity (17,18,28). The new focus from the National Institutes of Health on Translational Research could significantly benefit our basic understanding of the role of Lp(a) in mediating atherosclerosis and establish partnerships with pharmaceutical companies to define small molecules as therapies.

What are the gaps in clinical medicine and the rationale for developing targeted and specific therapies for lowering plasma Lp(a) levels? Despite the strong clinical data, randomized clinical trials documenting that lowering Lp(a) levels leads to clinical benefit have not been performed. Because specific and effective agents do not currently exist without affecting other lipoproteins, it is not going to be possible to test this hypothesis without development of novel Lp(a)-lowering agents. It is known that niacin and estrogens lower Lp(a) up to 30% but that statins either have no effect or increase Lp(a) levels, sometimes significantly (21). Recently, it has been shown that cholesteryl ester transport protein (CETP) inhibitors, thyroid mimetics, PCSK9 inhibitors, aspirin, and the antisense oligonucleotide to apoB, mipomersen (29), lower Lp(a) levels. However, in all these studies, Lp(a) levels were lowered in conjunction with changes in other lipoproteins. In the Women's Health Study, carriers of the *LPA* variant rs3798220 had doubling of cardiovascular risk and appeared to benefit more from aspirin than noncarriers (30). Additionally, the underlying mechanisms of Lp(a) lowering of these agents are not fully defined. We have recently demonstrated that a specific antisense oligonucleotide directed to KIV-II repeats lowers apo(a) mRNA and apo(a) plasma levels by 85% in apo(a)-transgenic mice, with minor effects

on other lipoproteins (27). Clinical development of this antisense oligonucleotide in which a mechanistic understanding of its action is known or other specific Lp(a)-lowering agents such as farnesoid X receptor agonists (31) will ultimately allow the testing of the hypothesis that elevated Lp(a) levels can be lowered substantially with concomitant reduction of cardiovascular events. The design of such a study would have to take into account LDL-C levels and other risk factors, but can be proposed and should be feasible with more specific and powerful Lp(a)-lowering agents. Initial potential subjects for such a trial could be patients with elevated Lp(a) (>25 to 30 mg/dl) and acute coronary syndromes that have high recurrence of repeat events, patients with familial hypercholesterolemia who generally have concomitantly high Lp(a) levels, more difficult to control LDL-C, and are at high risk for CVD events, and patients with mixed dyslipidemias and strong family history of CVD and patients with high Lp(a) and recurrent events despite maximal tolerated therapies. In conjunction with clinical trials, further validation of methodologies and standards in measuring and reporting Lp(a) are needed to optimize comparisons among studies (14). The recent recommendations of the European Atherosclerosis Society Consensus Panel (4) have suggested screening for elevated Lp(a) in those at intermediate or high CVD/coronary heart disease (CHD) risk, a desirable level <50 mg/dl as a function of global cardiovascular risk, and use of niacin for Lp(a) and CVD risk reduction. The latter 2 suggestions may be seen as controversial, as the evidence for niacin is only available from retrospective analyses, and the proper target for Lp(a) levels has not been established, but they provided a framework for ongoing debate and awareness of Lp(a) as a potential CVD risk factor. The National Lipid Association (32) has also recently provided a consensus document on screening moderate to high-risk patients for elevated Lp(a) levels. The recommendations of both of these societies will broaden the discussion of the role of Lp(a) in clinical care to detect and treat patients at risk and in investigational efforts to develop novel therapeutic agents.

Conclusions

The journey of Lp(a) as a clinically relevant lipoprotein over the last 50 years has evolved from an antigenic determinant in blood type, to a putative cardiovascular risk factor, to an independent, genetic risk marker of CVD. The next phase is to test causality as a risk factor by improved understanding of its biological functions and the development of novel and specific targeted therapies to assess reduction of cardiovascular outcomes and residual risk. We urge increased efforts to study the atherogenicity of Lp(a) by the academic and scientific communities, grant support by the National Institutes of Health and American Heart Association, and investment by the pharmaceutical industry. We look forward to the day when all lipoprotein disorders will have effective therapies to improve the quality of care for individuals and decrease risk of CVD.

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